Discussion Draft
American Chemistry Council

Perspectives On Tiered Exposure Assessment Within The EPA's VCCEP

INTRODUCTION

The EPA has always identified children as a subpopulation of concern for the evaluation of potential risks from exposures to chemicals. A pilot program to address that concern was announced by EPA in December 2000 called the Voluntary Children's Chemical Evaluation Program [VCCEP, Ref. 1]. The VCCEP includes hazard evaluation, exposure assessment and risk characterization components for each chemical to be evaluated. Data on the potential hazards of a particular chemical and information/data on the potential exposure of children to that same chemical will be developed in a tiered process and then integrated for a risk-based evaluation. Safety testing of chemicals is a reasonably well-prescribed process, but a major issue in implementing this risk-based program is the methodology of exposure assessment for estimating children's potential exposures. This document summarizes approaches to evaluating children's exposures in a way that parallels the tiered approach in the safety testing.

Concern for exposure to children has long been a focus for regulatory programs, with attention further increasing over the past decade. Since the mid-1980's EPA's Office of Drinking Water routinely evaluated exposure from oral ingestion of tap water for both adults and children, and EPA's current drinking water standards are designed to protect both children and adults (see EPA, 1999, Ref. 2). EPA's Office of Solid Waste has focused on pica behavior in children as a primary modality for assessing exposure from soil contamination at hazardous waste sites (EPA, 1989, Ref. 3). EPA's Office of Pesticide Programs focuses on children's dermal and non-dietary oral ingestion routes when evaluating residential exposures to pesticides (for example EPA, 1997, Ref. 4). In addition, the Office of Pesticide Programs requires a separate assessment of children's dietary exposure to crop protection chemicals under the Food Quality Protection Act of 1996. The US Food and Drug Administration has similar practices in place for estimating the risks to children from pediatric pharmaceutical chemicals.

This document discusses perspectives on developing exposure assessments for the pilot VCCEP. There is no single method or "cookbook" for developing exposure assessments applicable to all substances and all circumstances. Although the underlying principles to develop exposure assessments will be similar for different chemicals, each assessment will be unique. This document discusses the components relevant to developing exposure information within any of the three tiers of the VCCEP. Some or all of the components discussed in this document may or may not be relevant for a specific case. However, for all cases, the assessment must support a scientifically sound and satisfactory risk-based characterization for a given chemical for a given tier. Under certain circumstances the VCCEP indicates that sponsors may choose to focus submissions solely on hazard data elements (see VCCEP FR Notice (Ref. 1) for specifics). However, it is anticipated that most submittals for the VCCEP

will consider both hazard and exposure data. Critical components of an exposure assessment, at any tier, are scientific quality, completeness and transparency. It is expected that the data used and the assessment presented should be of high quality and as complete as necessary for the appropriate tier. Further, all calculations, model runs and derived estimates should be presented in a manner that provides sufficient information to allow a technically qualified person to make an independent evaluation of the assessment. This document is provided for the purpose of supporting consistency in reporting. Individual sponsors may adapt those relevant sections of the format that apply to their specific situations.

OVERVIEW OF EXPOSURE ASSESSMENT FOR THE VCCEP

A risk-based approach for evaluating potential health concerns from exposures to chemicals provides the scientific basis for ensuring that chemicals can be manufactured, transported, used and disposed of safely. Such a risk-based framework is incorporated in the EPA's VCCEP, wherein a tiered evaluation process is used to integrate data on the nature and magnitude of toxicity with information on the frequency, duration and level of exposure. Taken in its totality, this integrated risk-based evaluation would then be used to determine what, if any, additional specific toxicity tests or additional exposure appraisals are appropriate for specific substances to suitably characterize potential risks to children with an acceptable degree of scientific certainty.

A tiered exposure evaluation procedure is integral to such an approach. Exposure information can be developed in a tiered manner, commencing with screening methods and proceeding to more detailed exposure models and/or actual exposure measurements. Refined or detailed exposure evaluations provide greater certainty in the estimation of children's exposures. Thus, as indicated in the conceptual framework (Figure 1 from Ref. 1), at multiple points in this analytical paradigm, dose-response data from toxicity testing can be combined with exposure information to determine whether a chemical is adequately characterized or whether additional toxicity testing and/or additional exposure assessment efforts are warranted. If available, detailed exposure assessments can be integrated with available toxicity data at any decision point to evaluate potential hazards to children.

Exposure assessment is the process by which: (1) potentially exposed populations are identified; (2) potential pathways of exposure are identified; and (3) chemical intakes/potential doses are quantified. Exposure is dependent upon the magnitude, frequency, and duration of contact.

The basic steps for developing an exposure assessment specifically for children are the same as those used in any exposure assessment. Although exposure assessments for sensitive populations, including children, have long been integrated within chemical safety assessments conducted by government agencies and industry, the EPA's VCCEP requires

an explicit exposure assessment for children. The EPA's Guidelines for Exposure Assessment (EPA, Ref. 5, pg. 37) points out that an exposure assessment can be developed in three different ways:

> *1. The exposure can be measured at the point of contact (the outer boundary of the body) while it is taking place, measuring both exposure concentration and time of contact (i.e., exposure frequency and duration) and integrating them (point-of-contact measurement),*
>
> *2. The exposure can be estimated by separately evaluating the exposure concentration and the time of contact, then combining this information (scenario evaluation),*
>
> *3. The exposure can be estimated from dose, which in turn can be reconstructed through internal indicators (biomarkers of exposure, body burden, excretion levels, etc.) after the exposure has taken place (reconstruction).*

These three approaches to quantification of exposure are independent, because each is based on different data. As explained in greater detail by EPA (Ref. 5) the intended use of the exposure assessment will generally favor one method of quantifying exposure over the others. In many cases, for the EPA's VCCEP, the scenario evaluation approach (see #2 above) will be the preferred method; however, the use of other methods should not be precluded, as these may be determined to be most pertinent, especially for higher tiers. This method requires development of information on chemical concentrations in various media; this can be determined by sampling and analysis or by use of fate and transport models. Time and extent of contact data will require use of available information (i.e., default exposure factors), such as information provided by the recent EPA child-specific exposure factors handbook (http://www.epa.gov/ncea/csefh2.htm), and industry data, or development of new, scenario specific data. See Armstrong et al., 2000 (Ref. 6) for additional information concerning exposure pathway analysis and exposure assessments for children.

A discussion of the quality of exposure estimates is an important component of any exposure assessment. The quality of the exposure evaluation needs to be adequate to support the decision to be made. For example, in a screening level assessment one of the objectives is to decide whether the assessment supports a decision to assign a chemical or a particular pathway a low priority for further action. Furthermore, if a chemical or a pathway is not assigned a low priority in screening, understanding the quality is an important consideration when making a decision about what further work may be necessary.

While monitoring data are often preferred for estimating exposures, due to costs and other considerations, it is frequently the case that models are used instead. This is particularly the case in early assessment tiers. As a general rule, a well-designed and successfully implemented monitoring study is the preferred means of estimating exposures.

However, it would be scientifically unjustified and an oversimplification to say that monitoring data is always preferred over models. Exposure estimates based upon monitoring data vary in their quality and reliability, as do exposure estimates based upon models. Exposure estimates based upon models often use values for model inputs that have been derived from monitoring data, data measured in the laboratory, and other measured data to replace conservative default input values in the models. However, in some cases, a conservative model estimate of exposure is all that should be estimated because it is sufficient to answer the relevant assessment question (e.g. is there a concern for the exposure scenario) and the expense of collecting monitoring data would not be justified. In other cases, concerns for an exposure scenario cannot be eliminated using conservative assumptions and a more accurate estimate of exposure is needed. In this case, getting a more accurate exposure estimate by using a well designed study to collect monitoring data or validating an exposure model and using measured site or scenario-specific model inputs will increase costs, but may be necessary to address uncertainty.

The framework envisioned by EPA for the VCCEP for evaluation of toxicity testing data/information together with exposure data/information is illustrated below (excerpted from 12/26/00 FR Notice). Where a quantitative evaluation is performed, values should be presented in units that facilitate comparisons with relevant hazard data (e.g. mg/kg/day). It is recognized that *in utero* events have a bearing on children's health and the reproductive and developmental toxicity testing protocols included in the EPA's VCCEP framework directly address this concern. Development of exposure scenarios and evaluation of potential exposures for adults, such as occupational settings, would be envisioned when developmental and/or reproductive effects are identified in the toxicity tests. This would permit the hazard data to be represented in the context of exposure to the population of concern (e.g., prospective mother).

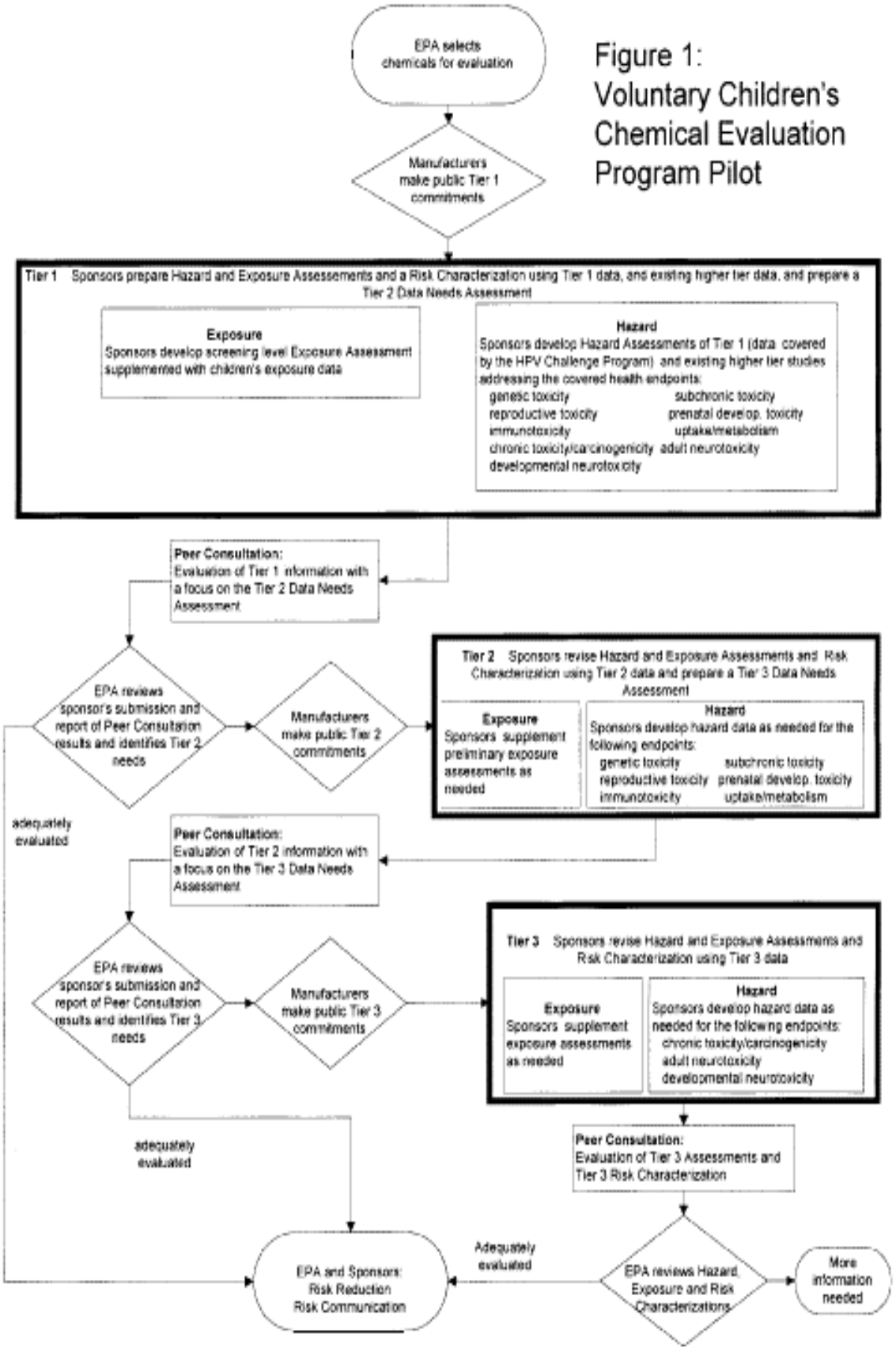

Figure 1: Voluntary Children's Chemical Evaluation Program Pilot

TIERED EXPOSURE ASSESSMENT METHODS

The EPA Guidelines for Exposure Assessment (Ref. 5, pg. 106) point out that most exposure assessments are done in a tiered or iterative manner, commencing with a screening approach. After each tier or iteration, the question is asked, was the degree of detail and/or confidence in the assessment adequate to achieve the purpose of the assessment? EPA's Guidelines for Exposure Assessment (Ref. 5, pg. 56) also acknowledge that the certainty or uncertainty in the toxicity evaluation can also guide the detail of an exposure assessment. For example, if the toxicity database is limited, a detailed in-depth exposure assessment "will in most cases be wasteful, since the most detailed information will not add significantly to the certainty of the risk assessment."

Tiered exposure assessments are often used in regulatory assessment of different populations' exposures to chemicals. The EPA's OPPT uses a tiered approach to develop exposure assessments (Ref. 7, http://www.epa.gov/opptintr/exposure/):

- "*Screening-level assessments that allow one to quickly prioritize exposures for further work; these assessments are based primarily on readily available data, conservative assumptions and simple models.*"

- "*Advanced assessments which focus on higher priority exposures that attempt to represent actual environmental conditions and exposures; these assessments require more data and make use of more sophisticated models or ideally, a well-designed monitoring study.*"

The goal of a tiered exposure assessment framework is to begin with less complex, default-driven, screening methods and to proceed, when necessary, to more complex, data-driven, chemical- and scenario-specific methods that reduce the uncertainty in estimates of exposure. In general, actual data is preferred in lieu of modeling, and to replace default assumptions. The best available data should be used. In some cases this will be measured data, in others modeled data, and in some cases a combination of the two. Measured concentration data obtained from a study that analyzed concentrations at the point of contact are, in general, preferable to model estimates. Consideration of temporal variations in concentration at the point of contact should be included, since concentrations can vary from location to location, seasonally, and over time due to changing release and use patterns. This needs to be considered when evaluating the applicability of using measured data for use in estimating exposures. Depending upon the certainty and reliability of the measured data, transport and dispersion models may be preferred.

The following three tiered exposure assessment approach conforms to EPA's treatment of exposure assessment in the VCCEP (see FR Vol 65, No. 248, 12/26/2000) and is consistent with the framework articulated by the Council (see ACC, 1999 (Ref. 8); Price, 1999 (Ref. 9)).

For each tier, an overview of the key human exposures evaluated should be provided in summary form. The exposure assessment should include a description and discussion of the types of potential exposures identified, the completeness of the evaluation, the methods used to estimate exposure (e.g., qualitative estimation, mathematical modeling, monitoring), the results, and a discussion of the accuracy and reliability of the exposure estimates.

During the process of stakeholder discussions regarding chemical testing for concerns over potential impacts on children's health, the American Chemistry Council proposed an evaluation framework that integrated toxicological data and exposure information to set testing priorities and to trigger additional testing. The Council's position on this point is that exposure data may be used in conjunction with available toxicity data when determining whether the substance should undergo specific laboratory toxicity tests to evaluate potential effects on children's health (see Ref. 8, ACC, 1999). The following discussion of tiered exposure assessment reflects background information and guidance developed by the Council on the matter of incorporating tiered exposure assessment into a risk-based framework for evaluation of chemicals to which children may be exposed.

Tier 1 Exposure Assessment

The methods cited by EPA's OPPT for screening level assessments (see http://www.epa.gov/opptintr/exposure/docs/screen.htm) were designed to overestimate exposure and inherently err on the side of health protection. Such methods calculate the upper bound exposure and are intended to be artificially high. OPPT states (http://www.epa.gov/opptintr/exposure/docs/screen.htm) that "[T]hese artificially high estimates mean that some substances will have exposure concerns where there actually are none; however, this bias provides a level of confidence that substances with exposure estimates indicating no concern are in fact not a concern.**"**

The FR Notice (Ref. 1) announcing the VCCEP states "At a minimum, the Tier 1 Exposure Assessment should contain screening level (or, if available, better) information on exposure from manufacturing supplemented with relevant screening level data on downstream processing and use activities and specific information on children's exposures, if available." Exposure information such as that generally contained in an OECD SIDS SIAR is one useful starting point for a screening level assessment. However, such information and data will need to be reviewed on a case-by-case basis to determine applicability for evaluating potential exposures to children. The components of a screening level exposure assessment are summarized in the box below:

Tier 1 -- Screening Level Exposure Assessment

- Begin with SIAR type approach; identify production volumes, major use functions/categories, potential sources of release to the environment, and physical form of the marketed product
- Obtain other readily available exposure data
- Identify potential pathways and routes of children's exposures
- Develop qualitative and semi-quantitative estimation of intakes based on conservative default assumptions
- Two steps:
  - Assess chemical concentration in medium
  - Estimate intake from child's contact with medium
- Set aside chemicals and specific pathways where intake(s)/dose(s) of toxicological concern is/are unlikely

Tier 2 and 3 Exposure Assessment

The advanced exposure assessment methodologies are designed to refine and more closely approximate the actual exposure and more accurately reflect the specific environments in which the exposures occur. The focus of advanced assessments is on the most sensitive sources and pathways identified in Tier 1. Using these methods will provide a more comprehensive exposure estimate with a greater level of relevance to the situation being evaluated than will screening methods. Where available, actual data are preferred for replacing default assumptions. Elements of an advanced exposure assessment should include consideration of the following:

Tier 2 -- Refined Exposure Assessment

- Refine critical source/pathway info
- If applicable, assess adult exposures based on reproductive/developmental data)
- Modify defaults with more realistic, scenario-specific data
- Incorporate variability and uncertainty in assessment
- Focus on most sensitive uses that dominate conservative estimates

Tier 3 -- Detailed Exposure Assessment

- In depth studies of critical sources or pathways
  - Evaluate detailed exposure related behaviors—habits and practices
  - Use better models of inter- and intra- individual variation
  - Use better data on temporal, spatial variation of source terms
- Combined monitoring and modeling approaches
  - Use monitoring data to confirm model predictions
  - Use modeling to extend/verify monitoring predictions

DEVELOPING EXPOSURE ASSESSMENTS

A wide variety of software packages are available or are in development for conducting exposure assessments. A review of exposure software for potential use in a tiered approach to assess exposures to children was prepared in late 1999 by Paul Price (Ref. 9). As noted by Paul Price (Ref. 9), there is no single software package that will address all potential routes for all chemicals. A flexible approach to the selection of the exposure assessment methods and software to address the chemical and situation specific concerns is recommended for the VCCEP. Additional screening level and higher tiered exposure models, which may be applicable for estimating children's exposures, are described by EPA (see Ref. 7, http://www.epa.gov/opptintr/exposure/).

Appendix A presents an outline for developing exposure information under the VCCEP. This guidance suggests elements to consider when developing and reporting exposure assessments for children, and is applicable to all of the tiers. It is vitally important to recognize that these will be case-by-case evaluations. Some elements may not be relevant for a given situation and it is not necessary to fully evaluate every element to arrive at a scientifically sound and adequate, risk-based characterization for a chemical. The document is provided only for the purpose of supporting consistency in reporting. Individual sponsors may adapt those relevant sections of the format that apply to their specific situation. Additional information relevant to the development of exposure assessments, as envisioned within the EPA's VCCEP, is provided in the EPA Guidlines for Exposure Assessment (Ref. 5), and the reports prepared by Paul Price (ref 9). Additional tools and guidance for gathering exposure information and conducting a variety of exposure assessments can be obtained from the Alliance for Chemical Awareness (Ref. 10) (http://chemicalawareness.org).

References

1. Federal Register: December 26, 2000 (Volume 65, Number 248)] Voluntary Children's Chemical Evaluation Program.

2. Children and Drinking Water Standards. EPA (1999) http://www.epa.gov/safewater/kids/child.pdf

3. Risk Assessment Guidance for Superfund (RAGS), Volume I -- Human Health Evaluation Manual, Part A, Chapter 6. EPA (1989) http://www.epa.gov/superfund/programs/risk/ragsa/index.htm

4. Pesticide Regulation (PR) Notice 97-1. EPA (1997) http://www.epa.gov/opppmsd1/PR_Notices/pr97-1.html

5. EPA Guidelines for Exposure Assessment - EPA/600Z-92/001. FR 57: 22888 - 22938. http://www.epa.gov/nceawww1/exposure.htm

6. Armstrong, TW, et al. [2000] Environ Health Perspec. 108(6) 469-474

7. EPA OPPT Exposure Assessment Tools and Models http://www.epa.gov/opptintr/exposure/

8. Comments of Chemical Manufacturers Association, 1999. An Alternative Toxicity Testing Approach for the EPA's Proposed Children's Health Chemical Testing Program

9. Price, P. An Evaluation of the Potential of Current Exposure Software for Use in a Tiered Approach to the Assessment of Exposures and Risk to Children, 1999. (Report prepared for CMA, available upon request)

10. Alliance for Chemical Awareness, http://chemicalawareness.org/

Appendix A – Page A-1
Outline for Assessing Potential Presence of a Chemical in Children's Environments

- ***This guidance suggests elements to consider when developing and reporting exposure assessments for children. It is vitally important to recognize that these will be case-by-case evaluations.***

- ***These elements do not correspond to any specific tier. Some elements may not be relevant for a given situation and it is not necessary to fully evaluate every element to arrive at a scientifically sound and adequate risk-based characterization for a chemical.***

- ***The document is provided for the purpose of supporting consistency in reporting. Individual sponsors may adapt those relevant sections of the format that apply to their specific situation.***

Chemical Identity

- *Substance Identification*
  Include CAS RN, Chemical Name, Synonyms, molecular and structural formulas, purity and identity/concentration of other constituents. Also include any pertinent, test substance-specific remarks.

Source of Exposure Information

- *Identification* (*Company,* Consortia, or Other)
  Include all relevant contact information including technical contact name, phone and fax numbers, and address. Detail any specific information on the source specific to this exposure information. If the source is "Other," please provide name and full address.
- *Date*

Properties, Uses and Basic Exposure Information

- *Physical and chemical properties*
  SIDS data—melting point, boiling point, vapor pressure, water solubility, log Kow and ionization, persistence and bioaccumulation potential, or other relevant data.

- *Environmental fate*
  SIDS data—photodegradation, biodegradation, transport and degradation, stability in water, etc.

- *Annual Volume* (Produced and Imported)
  Report as approximate quantity with indication of accuracy or as a range (e.g., 1000 to 10,000 tons).

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- *Community-Related Exposures: Site Release and Disposal*

- *Product Related Exposures:*

  For a Tier 1 exposure assessment the objective is to identify major and relevant uses to the extent necessary to develop exposure point concentrations for a screening level evaluation.

  Use Patterns:
  For example, identify Use patterns among Intermediate, Industrial, Commercial and Consumer uses as appropriate with approximate percent or range of percent of the total volume that falls within the type:

  Intermediate
  Industrial
  Commercial
  Consumer

  Product Use Categories
  For example, identify specific Product Use Categories representing commercial or consumer uses and approximate percent or range of percent of the total volume that falls within the category. Applying the form on page A-4 can provide insight about potential children's exposures related to that use.

  - *Other Non-manufacturing Sources of Exposure*
    Describe other non-manufacturing sources of exposure, types, amount of substance, media, and estimates of data quality, reliability and uncertainty, if available.

Estimated Exposure Potential—Quantitative
Describe the method(s) used to estimate exposures including, as appropriate, citations of exposure data/studies used, models used, default scenarios, equations and parameter values. When available, chemical and scenario specific data/approaches are encouraged over default values.

- *Product Related Human Exposure*
  Estimates of the exposures to children who use or are exposed to specified product(s), which includes an indication of the reliability or uncertainty, if available.
- *Environmental Exposure (for use in estimating Indirect Human Exposure*
  Estimates of environmental exposures. These estimates should include an indication of the reliability or uncertainty, if available.
- *Indirect Human Exposure*
  Estimates of indirect exposure to children, including an indication of the reliability

or uncertainty, if available.

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- *Other Non-manufacturing Source-related Human Exposure*
  Estimates of non-manufacturing source exposure to children, including an indication of the reliability or uncertainty, if available.

Measured Exposure (if available) Indicate what, where, when and how many data points and include information on the data quality, reliability and uncertainty, if available.

- *Product/End-use Exposure to humans.*
- *Environmental Exposure*
- *Indirect Exposure to humans.*

- *Other Non-manufacturing Source-related Human Exposure.*

Discussion of VCCEP selection data source information

- *Bio-monitoring and environmental monitoring data*
  Indicate what, where, when (i.e., date of study) and how many data points and include information on the data quality, reliability and uncertainty.

Overall Weight of Evidence Assessment of Potential for Exposure to Children

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CAS Number _____ Company_____
Chemical Name _____

FOR END USES OTHER THAN AS A CHEMICAL INTERMEDIATE

Product Use Category/Subcategory-Product Type _____

Approximate percent of total manufactured and imported volume going to this use
____% +/-___%

Setting for use of this Product: (indicate all that apply and specifics where appropriate)
Indoor _____ Outdoor _____

Industrial __	**Commercial __**	**Institutional __**	**Residential __**
(e.g. Non-isolated intermediate)	(e.g. grocery, retail store, gas station, dry cleaner)	(e.g. day care, pre-school, elementary, secondary, hospital)	Intended for children___ Potential for children's exposure____ No potential for children's exposure____

If chemical is used in a mixture, indicate weight fraction	**Indicate predominant physical forms of the chemical during this use**
__ <0.1% __ 0.1-1% __ 1-10% __ 10-25% __ 25-50% __ 50-75% __ >75% Specify actual range if known _____	__ Aerosol __ Dry Powder __ Pellets or large crystals __ Water or solvent-wet solid __ Gas or Vapor __ Liquid Solution __ In Solid Matrix __ Other (explain)_____

Extent of Exposure
(indicate all that apply)

Age(s) of Child(ren)	**Likely Route of Exposure**
__ *0 – 6 mo*	__ Inhalation
__ *6mo – 2 yr*	__ Oral
__ *2 – 5*	__ Dermal
__ *5 – 12*	__ Other
__ *12 – 18*	

Likely Duration of Exposure	**Likely Frequency of Exposure**
__ Seconds	__ 1 – 2x per yr
__ Minutes	__ 1 – 2x per mo
__ < 1 hr	__ 1 – 2x per wk
__ 1-8 hrs	__ 1 – 2x per day
__ > 8hrs	__ > 2x per day